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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,745	CASIMIR, COLIN MAURICE	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-45,47,48 and 50-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-45,47,48 and 50-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/05/2009 has been entered.

Claims 1-42, 46, 49, and 57-67 are cancelled. Claim 43 is amended. Claims 43-45, 47, 48 and 50-56 are pending and currently under examination.

This application 10/520,745 filed on Aug. 22, 2005 is a 371 of PCT/GB03/03012 filed on 07/11/2003.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. Previous rejection of claims 43-45, 47, 48 and 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is ***withdrawn*** because independent claim 43 has been amended.

Claim 43 has been amended and no longer recites two contradicting limitations in step (ii): limitation "expressing the viral nucleic acid and nucleic acid encoding the passenger peptide binding moiety and incorporating said passenger peptide binding moiety into said packaging cell

membrane ---" and limitation "wherein the passenger peptide binding moiety is other than a chimeric or fusion protein and wherein said passenger peptide is other than one derived from the virus or said packaging cell". Claims 44, 45, 47, 48 and 50-56 depend from claim 43.

2. Claims 43-45, 47, 48 and 50-56 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments by Applicant filed on 11/11/2008.*

Claim 43 has been amended to recite in step (ii) "wherein the passenger peptide binding moiety is selected from the group consisting of cell growth factors, antibodies or antigen-binding fragments thereof, moieties that recognize a target cell-- specific surface antigen, and moieties that are at least a part of a member of a binding pair comprising a target -- cell specific cell -- surface receptor and its ligand and wherein said passenger peptide is other than one naturally derived from the virus or said packaging cell". It is unclear how this limitation should be read with proper punctuation in the presence of three "--" signs. Applicant is advised to clarify what the three "--" signs are intended to mean.

Additionally, claim 43 has been amended to recite "(ii) expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane and a viral particle buds from said packaging cell membrane". The metes and bounds of the limitation "the passenger peptide binding moiety is provided at a cell membrane" cannot be determined in light of the recitation of "a viral packaging cell" in the same claim. It is unclear whether "a cell" of phrase "a cell

membrane" recited in line 5 of amended step (ii) is "a viral packaging cell" recited in line 1 of step (i). Accordingly, claim 43 simultaneously recites two different scopes of cells in step (i) versus in step (ii).

Moreover, independent claim 43 is unclear as it fails to relate back to the preambles in a positive process. In this regard, the preamble of claim 43 recites "A method of making a viral particle having modified cell binding activity", which indicates "a modified cell binding activity" is required by the claimed method. However, the limitation "allowing the passenger peptide binding moiety to be incorporated into the viral particle to modify its first cell binding activity" in step (ii) of claim 43, does not require "a modified cell binding activity" recited in the preamble of claim 43 to occur. In other words, incorporation of a passenger peptide into a viral particle does not necessarily result in "a modified cell binding activity" in said viral particle. More discussions in this regard are provided in the maintained scope of enablement rejection under the first paragraph of 35 USC.

Claims 44, 45, 47, 48 and 50-56 depend from claim 43.

Claim Rejection – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 43-45, 47, 48 and 50-56 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for **(I)** a method of making a retroviral particle having a modified cell binding activity by genetically modifying envelope proteins of the

retroviral particle, and enabling for **(II)** a method of making a retroviral particle having a modified cell binding activity without genetically modifying envelope proteins of the retroviral particle, comprising the steps of providing a retroviral packaging cell, wherein the retroviral packaging cell contains viral nucleic acid encoding an enveloped viral particle that is unable to naturally bind to a target cell; and transfecting said retroviral packaging cell line with an expression vector comprising a heterologous nucleic acid sequences encoding membrane bound human stem cell factor (mbSCF) operably linked to an eukaryotic promoter such that human mbSCF is expressed on the membrane of the packaging cell wherein a resulting retroviral particle produced from said packaging cell bears human mbSCF on the envelope of the retroviral particle that directs the binding of the retroviral particle to a target cell expressing c-kit on the membrane of said target cell, **does not** reasonably provide enablement the said method without genetically modifying envelope proteins of the retroviral particle [i.e. abovementioned **(II)**] for **(i)** a nucleic acid encoding any peptide binding moiety other than human stem cell factor (SCF), or **(ii)** any target cell other than the target cell expressing c-kit receptor on its cell membrane, or **(iii)** a method comprising steps of making a retroviral particle having a modified cell binding activity, wherein the modified cell binding activity of said retroviral particle is determined by any non-Envelope-receptor interactions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

It is noted the maintained scope of enablement rejection has been revised to address the claim amendments filed on 11/11/2008, which deletes limitation "is other than a chimeric or fusion protein" in step (ii) of claim 43, and recites "wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety designed to modify said first cell binding activity of said viral particle" in step (i) of claim 43.

Relevant to the claim amendment by deletion of the limitation "is other than a chimeric or fusion protein in step (ii) of claim 43, the added enabled embodiment pertaining to a method of making a viral particle having a modified cell binding activity by genetically modifying envelope proteins of the viral particle is necessitated by this claim amendment and is supported by the disclosure of the specification of instant application (See paragraph [0013], US 2006/0110361, publication of instant application) as well by the status of art. In this regard, the 102(a) rejection by Gollan et al. (2002) documented in this office action provides an example.

Relevant to the claim amendment of "exogenous nucleic acid", it is worth noting that viral genome and extra-chromosomal nucleic acid introduced into a given viral packaging cell are considered exogenous to the endogenous genomic DNA of the viral packaging cell. More elaboration in this regard is provided in the prior art rejection of this office action.

Applicant's arguments filed 11/11/2008 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 5-12 of the Non-Final office action mailed on 11/19/2007, and elaborated on pages 4-16 of Final office action mailed on 09/12/2008.

The basis for maintaining the rejection are summarized as follows: (1) as alluded in the 112 second rejection documented in this office action, incorporation of a passenger peptide into a viral particle does not equal to "modified cell binding activity" in said viral particle, and (2) "modified cell binding activity" (i.e. altered tropism) of viral particle depends on many parameters. More discussions are provided below.

As elaborated on pages 4-16 of Final office action mailed on 09/12/2008, the issues contributing to the lack of predictability revealed in the prior arts and identified in the previous Non-Final rejection mailed on 11/19/2007 include (a) the size limitation and resulting intracellular location of any given passenger peptide binding moiety (including a non-cell membrane bound peptide) other than membrane bound human SCF that can be expressed from the packaging cell such that the passenger peptide binding moiety is incorporated into the envelope of a given retroviral particle, (b) cross interaction between a passenger peptide binding moiety and a receptor (or receptors) affecting recited modified cell binding activity" (i.e. altered tropism) of a viral particle, a process involving the topology and expressed levels of the

introduced passenger peptide binding moiety in the viral envelope and the topology and expressed levels of its corresponding receptor(s) present on the cell surface under a given growth condition, (c) viral tropism determined by contacts between viruses and cell occur outside of the *bona fide* Env-receptor interaction, and (d) potential immune and inflammation responses as a result of introduced passenger peptide binding moiety and other cell-derived components being associated with viral vector particle.

Applicant's Arguments and Response to Applicant's arguments

Applicant's previous arguments filed on 05/20/2008 regarding (i) incorporation of membrane proteins into viral particle, (ii) the properties of membrane proteins to be incorporated into viral particle, (iii) binding properties of membrane proteins, and (iv) immune and inflammatory responses, and (v) the viral envelope is not modified, and the Examiner's response to these arguments have been documented on pages 7-16 of the Final office action mailed on 09/12/2008. It is worth noting that the claim amendments filed on 11/11/2008, which includes the deletion of limitation "is other than a chimeric or fusion protein" in step (ii) of claim 43, have rendered previous argument "(v) the viral envelope is not modified" no longer applicable to the amended claim 43 filed on 11/11/2008.

In the reply filed on 11/11/2008, Applicant states that Applicant remains convinced that, with respect to the incorporation of membrane proteins into budding viral particles, it is well established, for example in Hammarstedt et al (2000), that the majority of proteins present on the cell surface become incorporated into retroviral particles. Further, with respect to the Hammarstedt et al article, that article was cited to show that most membrane proteins are

incorporated into budding viral particles, not that the binding affinity of such particles are modified by those membrane proteins. Thus, the article was not cited to support the claimed "modified cell binding activity" of the current invention as the Examiner appears to believe. Applicant states that Applicant further believes that the limitations of the scope of the passenger peptide added to claim 43 renders the claim both predictable with respect to folding and incorporation of the passenger peptide and incorporation of the passenger peptide into the viral particle, having the affect of modifying the binding activity of the resultant viral particle (See page 7-8 of Applicant's reply filed on 11/11/2008).

In response, the Examiner acknowledge and agree with Applicant statements that Hammarstedt et al article shows that most membrane proteins are incorporated into budding viral particles, not that the binding affinity of such particles are modified by those membrane proteins. Accordingly, the Examiner maintains the position that the report by Hammarstedt et al. (2000) on association of plasma membrane proteins with retroviral particles fails to support the claimed "modified cell binding activity" of the retroviral particle. Relevant to this issue, it is worth emphasized again that, in the art, as discussed on page 11 of Non-Final office action mailed on 09/05/2006, how a virus infects its host cell is determined by many factors including, but not limited to, the interactions between viral envelope proteins and receptor/co-receptor proteins on cell surface. **Manel et al.** reviewed the HTLV-1 tropism and envelope receptor stated, "---tropism depends on many parameters that are independent of Env-receptor interactions, ---"(page 6022, right column, third paragraph under Conclusions and perspectives, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene*. 24(39): 6016-25, 2005). For instance, "contacts between viruses and cell also occur outside of the *bona fide* Env-receptor interactions that lead to

productive viral replication" (page 6016, right column, second paragraph, Manel et al., HTLV-1 tropism and envelope receptor. *Oncogene*. 2005 24(39): 6016-25, 2005). Furthermore, even in the case of more conventional approach when the viral envelope proteins are genetically altered, it is unpredictable how a given change in the envelope, which is the main determinant of viral tropism, would lead to modified cell binding activity of the viral particles as claimed in instant application. In this regard, **Gollan et al.** discloses that when insertions of short RGD-containing peptides, which are ligands for integrin receptor, into the envelops of Moloney murine virus (MLV, a retrovirus), the precise location, size, and flanking sequences of the ligand affects transduction specificity and efficiency (See abstract, Figures 1-4, Gollan et al., Redirecting retroviral tropism by insertion of short, non-disruptive peptide ligands into envelope, *J Virol.* 76(7):3558-63, 2002).

As an additional layer of unpredictability pertaining to the binding properties of a passenger peptide and potential modification of viral envelope by association with claimed "passenger peptide", it has been documented on pages 12-24 of the Final office action mailed on 09/12/2008 that for a given membrane protein to be functional, it requires proper expression, modification, protein folding, incorporation into a given membrane environments etc. To demonstrate the foundation of this aspect of the rejection, **Parmley et al.**, 2007, teaches that even silent SNPs (single nucleotide polymorphisms) encoding the same amino acid residues are not necessarily neutral with regard to their effects on the functions of polypeptides, and there are two additional mechanisms affecting the function of a given polypeptide: (1) modification of protein structure and activity, mediated by induction of translational pausing during co-translational protein folding, and (2) modification of protein abundance mediated by alteration in

mRNA stability via changed secondary structures of mRNA, which in turn leads to perturbation in protein synthesis (See abstract, Parmley et al., How do synonymous mutations affect fitness? *Bioessays*, 29(6): 515-9, 2007). In other words, alterations in either protein folding or translational efficiency result on changed protein functions encoded by synonymous mutations. This has been clearly demonstrated in the membrane bound P-glycoprotein, which **Kimch-Sarfaty et al.** reports that a "silent" polymorphism in the MDR1 gene change substrate specificity of the encoded P-glycoprotein (See Kimch-Sarfaty et al. A "silent" polymorphism in the MDR1 gene changes substrate specificity. *Science*, 315(5811):525-8, 2007). Therefore, Applicant previous arguments filed on 05/20/2008 that properties of the passenger peptide, such as charge, folding, post-translational modification, hydrophobicity, etc. would have no relevance in terms of its incorporation into the viral particle membrane, are not persuasive because binding properties of a given membrane protein exemplifies the function of the membrane protein (i.e. the claimed "passenger peptide"). Applicant's reply filed on 11/11/2008 does not provide any new argument pertaining to this layer of unpredictability in the art. Accordingly, Applicant's assertion/belief in reply filed on 11/11/2008 fails to overcome the unpredictability of the status of art. Thereby, as documented in the maintained rejection, the claimed method is only enabled for the disclosed example when membrane-bound form of human stem cell factor (mbSCF) is expressed on the membrane of a retroviral packaging cell wherein a resulting retroviral particle produced from said retroviral packaging cell bears human mbSCF on the envelope of the retroviral particle that directs the binding of the retroviral particle to a target cell expressing c-kit receptor on the membrane of said target cell.

In conclusion, the Examiner maintains the position that, the specification as filed fails to provide any specific guidance and/or working examples, regarding non-retroviral particles, and the specification also fails to direct the skilled artisan to any teachings on the relationship between the control of the expression level of a passenger peptide binding moiety and its incorporation into viral particles, and how the relationship may affect the recognition between a passenger peptide and its receptor, and the infectivity the viral particles to specific target cells, which would allow one of skill in the art to make and use the claimed invention without undue experimentation. In view of the state of the unpredictability in the art, and the lack of guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention commensurate in scope with the claims 43-45, 47, 48, and 50-56.

Claim Rejection – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Previous rejection of claims 43-45, and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000), is ***withdrawn*** because the claims have been amended.

Claim 43 has been amended to read as follows: A method of making a viral particle having a modified cell binding activity comprising:(i) providing a viral packaging cell containing viral nucleic acid encoding an enveloped viral particle, wherein said viral particle is enveloped using an envelope unable to naturally bind to cells of a species being targeted, said viral particle having a first cell binding activity wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety designed to modify said first cell binding activity of said viral particle; (ii) expressing the viral nucleic acid and exogenous nucleic acid encoding the passenger peptide binding moiety so that the passenger peptide binding moiety is provided at a cell membrane and a viral particle buds from said packaging cell membrane thereby allowing the passenger peptide binding moiety to be incorporated into the viral particle to modify its first cell binding activity, wherein the passenger peptide binding moiety is selected from the group consisting of cell growth factors, antibodies or antigen-binding fragments thereof, moieties that recognize a target cell-specific surface antigen, and moieties that are at least a part of a member of a binding pair comprising a target-cell specific cell-surface receptor and its ligand and wherein said passenger peptide is other than one naturally derived from the virus or said packaging cell.

It is noted that each of the three "--" signs in amended claim 43 is interpreted as "-" (See underlined phrases in the preceding paragraph. Soong et al. does not teach the following amended limitations: (i) wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety, and (ii) wherein the passenger peptide binding moiety is selected from the group consisting of cell growth factors, antibodies or antigen-binding fragments thereof, moieties that recognize a target cell-specific surface antigen, and moieties that

are at least a part of a member of a binding pair comprising a target-cell specific cell-surface receptor and its ligand. Claims 44, 45, 54-56 depend from claim 43.

5. Claims 43-45, 54, and 55 are rejected under 35 U.S.C. 102(a) as being anticipated by Gollan et al., Redirecting retroviral tropism by insertion of short, non-disruptive peptide ligands into envelope, *J Virol.* 76(7):3558-63, 2002). *This rejection is necessitated by claim amendments filed by Applicant on 11/11/2008.*

Claim interpretation: The limitation "wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety" recited in claim 43 reads on any viral genome because the viral genomic nucleic acids are exogenous to the endogenous genomic DNA of the viral packaging cell. The interpretation that the breadth of claim 43 encompasses any viral genome encoding claimed "passenger peptide" is supported by claim 56, which recites further limitation "wherein the modified cell binding activity is conferred by a peptide other than a chimeric viral envelopes polypeptide".

Gollan et al. teaches that potentially powerful approach for *in vivo* gene delivery is to target retrovirus to specific cells through interactions between cell surface receptors and appropriately modified viral envelope proteins. Gollan et al. teaches that, relatively large (>100 residues) protein ligands to cell surface receptors have been inserted at or near the N terminus of retroviral envelope proteins; and although viral tropism could be altered, the chimeric envelope proteins lacked full activity, and coexpression of wild-type envelope is required for production of transducing virus. Gollan et al. analyzes more than 40 derivatives of ecotropic Moloney murine leukemia virus (MLV) envelope, containing insertions of short RGD-containing peptides, which

are ligands for integrin receptors, and in many cases pseudotyped viruses containing only the chimeric envelope protein could transduce human cells. Gollan et al. teaches that the precise location, size, and flanking sequences of the ligand affected transduction specificity and efficiency, and concludes that retroviral tropism can be rationally reengineered by insertion of short peptide ligands and without the need to coexpress wild-type envelope (See abstract, Gollan et al., Selective targeting and inducible destruction of human cancer cells by retroviruses with envelope proteins bearing short peptide ligands, *J Virol.*, 76(7):3564-9, 2002).

With regard to the limitation of claim 44 reciting "the peptide binding moiety is provided at an outer plasma membrane of the cell, it is noted that during the process of viral budding from the packaging cell the viral envelope proteins are provided at the outer membrane of the packaging cell.

Thus, Gollan et al. clearly anticipates claims 43-45, 54, and 55 of instant application.

6. Claims 43-45, 47, and 54-56 are rejected under 35 U.S.C. 102(b) as being anticipated by **Povey et al.** (Povey et al., Enhanced retroviral transduction of 5-fluorouracil-resistant human bone marrow (stem) cells using a genetically modified packaging cell line, *Blood*, 92(11):4080-9, 1998) as evidenced by **Hammarstedt et al.** (Hammarstedt et al. Minimal exclusion of plasma membrane proteins during retroviral envelope formation. *Proc Natl Acad Sci U S A.* 97(13):7527-32, 2000; this reference has been provided as Exhibit A in the Applicant's remarks filed on 05/20/2008). *This rejection is necessitated by claim amendments filed by Applicant on 11/11/2008.*

It is noted that Hammarstedt et al. (2000) reference has been provided as Exhibit A in the Applicant's remarks filed on 05/20/2008. However, this reference has not been listed either on considered IDS or PTO-892 form cited by the Examiner. For clarity of record, this reference is listed in the attached PTO-892 form attached with this office action.

Claim interpretation: The limitation "wherein the viral packaging cell also contains exogenous nucleic acid encoding a passenger peptide binding moiety" reads on any extra-chromosomal nucleic acid introduced into a given viral packaging cell because extra-chromosomal nucleic acids are exogenous to the endogenous genomic DNA of the viral packaging cell.

Povey et al. teaches constructed a retroviral producer line (1MI-ΔSCF) that expresses the membrane-bound form of human stem cell factor (SCF) on its cell surface (See bridging paragraph, pages 4081-4082, and Figure 1, provided below, Povey et al., *Blood*, 92(11):4080-9, 1998).

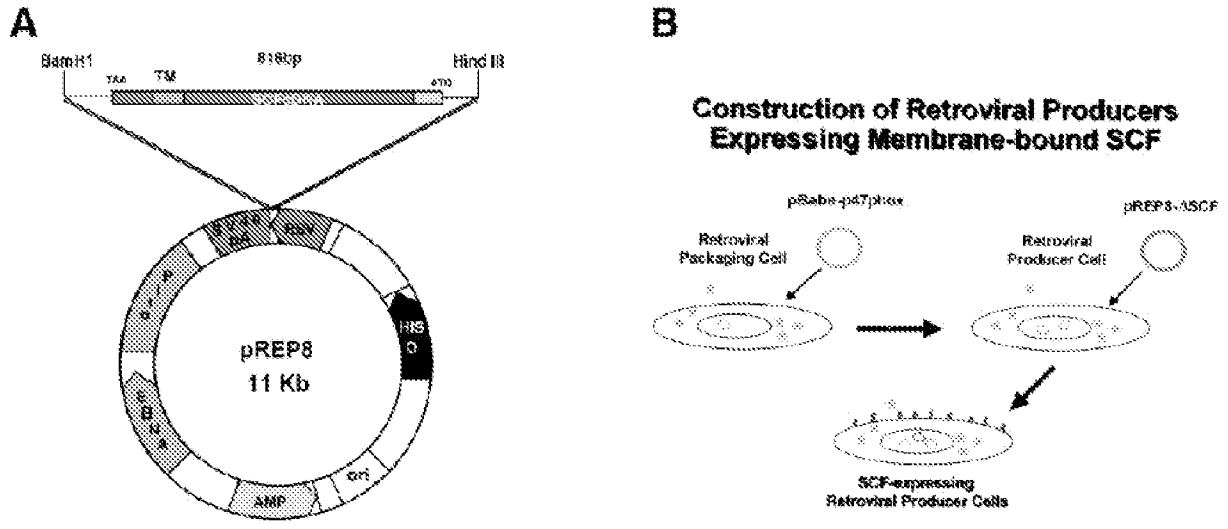


Fig 1. Construction of retroviral producer cells expressing membrane-bound SCF. (A) Schematic of plasmid pREP8-ΔSCF. (B) Evolution of cell line 1MI-ΔSCF from AM12 packaging line.

Povey et al. the retroviral transduction frequency of the quiescent 5-fluorouracil (FU) resistant bone marrow cells using the SCF-expressing producer line averaged about 20%, whereas those transduced using the retroviral particle obtained from parent producer line showed evidence of reduced levels or no transduction (See page 4084 and Figure 3, Povey et al., *Blood*, 92(11):4080-9, 1998).

Povey et al. does not explicitly teach that the SCF (i.e. a passenger peptide binding moiety encoded by exogenous nucleic acid recited in claim 43 of instant application) is allowed to be incorporated into the viral particle, which in turn may account, at least in part, for the increased retroviral transduction frequency using the SCF-expressing producer line.

However, Hammarstedt et al. teaches that the retrovirus forms its envelope by budding at the plasma membrane (PM), and this process is primarily driven by its cytoplasmic core-precursor protein, Gag, as shown by the efficient formation of virus-like Gag particles in the absence of its envelope protein, Env. Hammarstedt et al. teaches the purification of Moloney murine leukemia virus Gag particles by sedimentation in an iodixanol gradient and donor PMs by flotation in a sucrose gradient and compared their protein compositions at equal lipid basis, and found that most PM proteins are present at similar density in both membranes. Hammarstedt et al. teaches the inclusion of PM proteins was unaffected by incorporation of Env protein into the envelope of the Gag particles and whether these were produced at high or low level in the cells. Hammarstedt et al. concludes that these findings indicate that PM proteins become incorporated into the retrovirus envelope without significant sorting, and this feature of retrovirus assembly should be considered when studying retrovirus functions and developing retrovirus vectors.

The teachings by Hammarstedt et al. clarify that the retroviral particles produced from the SCF-expressing producer line taught by **Povey et al.** will inherently allow the SCF, expressed on the plasma membrane of the retroviral packaging cell, to be incorporated into the retroviral particles when the viral particle buds from the retroviral packaging cell, as recited in claim 43 of instant application.

Thus, Povey et al. as evidenced by Hammarstedt et al. clearly anticipates claims 43-45, 47, and 54-56 of instant application.

Claim Rejection – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Previous rejection of claims 43, 48, 50 and 51 under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. *Nature* 25(4): 436-9, 2000) in view of Dropulic et al. (U.S. patent No. 6,114,141, issued Sep. 5, 2000; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006), is ***withdrawn*** because the claims have been amended.

Soong et al. does not the limitations of amended claim 43 as discussed in the withdrawn rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al.

(2000). Dropulic et al. does not teach the limitations of amended claim 43 filed by Applicant on 11/18/2008, thereby Dropulic et al. cannot remedy the deficiency of Soong et al.

8. Previous rejection of claims 43, 48, 52 and 53 under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000) in view of Guber et al. (U.S. patent No. 569,177, issued Nov. 25, 1997; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006), is ***withdrawn*** because the claims have been amended.

Soong et al. does not the limitations of amended claim 43 as discussed in the withdrawn rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al. (2000). Guber et al. does not teach the limitations of amended claim 43 filed by Applicant on 11/18/2008, thereby Guber et al. et al. cannot remedy the deficiency of Soong et al.

9. Previous rejection of claims 43 and 47 under 35 U.S.C. 103(a) as being unpatentable over Soong et al. (Soong et al., Molecular breeding of viruses. 25(4): 436-9, 2000) in view of Yajima et al. (Retroviral vector targeting human cells via c-Kit-stem cell factor interaction. *Hum Gene Ther.* 9(6): 779-87, 1998; listed as the last reference in the IDS filed on 05/04/2007), is ***withdrawn*** because the claims have been amended.

Soong et al. does not the limitations of amended claim 43 as discussed in the withdrawn rejection of claims 43-46 and 54-56 under 35 U.S.C. 102(b) as being anticipated by Soong et al.

(2000). Yajima et al. does not teach the limitations of amended claim 43 filed by Applicant on 11/18/2008, thereby Yajima et al. cannot remedy the deficiency of Soong et al.

10. Claims 43, 48, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Povey et al.** (Povey et al., Enhanced retroviral transduction of 5-fluorouracil-resistant human bone marrow (stem) cells using a genetically modified packaging cell line, *Blood*, 92(11):4080-9, 1998) in view of **Hammarstedt et al.** (Hammarstedt et al. Minimal exclusion of plasma membrane proteins during retroviral envelope formation. *Proc Natl Acad Sci U S A.* 97(13):7527-32, 2000) and **Dropulic et al.** (U.S. patent No. 6,114,141, issued Sep. 5, 2000; listed in the PTO-892 in Non-Final rejection mailed on 09/05/2006). *This rejection is necessitated by claim amendments filed by Applicant on 11/11/2008.*

Povey et al. teaches constructed a retroviral producer line (1MI-ΔSCF) that expresses the membrane-bound form of human stem cell factor (SCF) on its cell surface (See bridging paragraph, pages 4081-4082, and Figure 1, provided below, Povey et al., *Blood*, 92(11):4080-9, 1998).

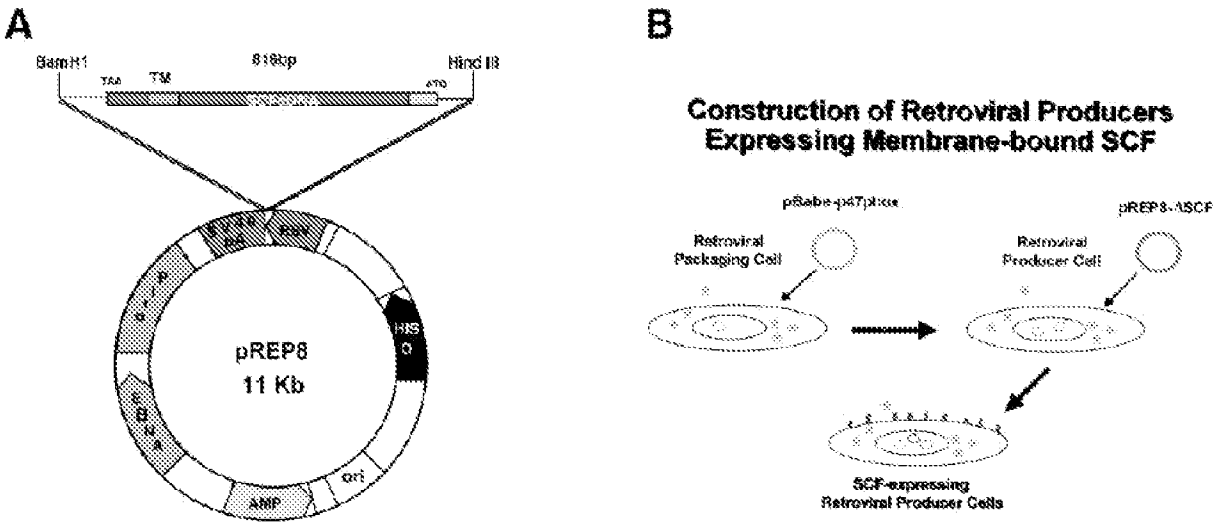


Fig 1. Construction of retroviral producer cells expressing membrane-bound SCF. (A) Schematic of plasmid pREP8-ΔSCF. (B) Evolution of cell line 1MI-ΔSCF from AM12 packaging line.

Povey et al. the retroviral transduction frequency of the quiescent 5-fluorouracil (FU) resistant bone marrow cells using the SCF-expressing producer line averaged about 20%, whereas those transduced using the retroviral particle obtained from parent producer line showed evidence of reduced levels or no transduction (See page 4084 and Figure 3, Povey et al., *Blood*, 92(11):4080-9, 1998).

Povey et al. does not explicitly teach that the SCF (i.e. a passenger peptide binding moiety encoded by exogenous nucleic acid recited in claim 43 of instant application) is allowed to be incorporated into the viral particle, which in turn may account, at least in part, for the increased retroviral transduction frequency using the SCF-expressing producer line.

However, Hammarstedt et al. teaches that the retrovirus forms its envelope by budding at the plasma membrane (PM), and this process is primarily driven by its cytoplasmic core-precursor protein, Gag, as shown by the efficient formation of virus-like Gag particles in the absence of its envelope protein, Env. Hammarstedt et al. teaches the purification of Moloney murine leukemia virus Gag particles by sedimentation in an iodixanol gradient and donor PMs

by flotation in a sucrose gradient and compared their protein compositions at equal lipid basis, and found that most PM proteins are present at similar density in both membranes. Hammarstedt et al. teaches the inclusion of PM proteins was unaffected by incorporation of Env protein into the envelope of the Gag particles and whether these were produced at high or low level in the cells. Hammarstedt et al. concludes that these findings indicate that most PM proteins become incorporated into the retrovirus envelope without significant sorting, and this feature of retrovirus assembly should be considered when studying retrovirus functions and developing retrovirus vectors.

The teachings by Hammarstedt et al. indicates that the retroviral particles produced from the SCF-expressing producer line taught by **Povey et al.** inherently allow the SCF, expressed on the plasma membrane of the retroviral packaging cell, to be incorporated into the retroviral particles when the viral particle buds from the retroviral packaging cell, as recited in claim 43 of instant application.

Neither Povey et al. nor Hammarstedt et al. teaches additional nucleic acid which can express any one of the bioactive agent selected from ricin, tumor necrosis factor, interleukin-2 (a cytokine), interferon-gamma, ribonuclease, deoxyribonuclease, pseudomonas exotoxin A and caspase.

With regard to claim 43, 48, 50 and 51, Dropulic et al. teach methods to express genes from viral vectors (See title and abstract). Specifically, Dropulic et al. teach the expression of antiviral agent including a cytokine, a single-chain antibody, a cellular antigen or receptor (See claims 4 and 21).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Dropulic et al. regarding expressing a cytokine (interleukine-2) from a viral vector into the combined teachings of Povey et al. and Hammarstedt et al. regarding the method of generating a retrovirus with altered tropism and to achieve the claim 51 of instant application on a method of making a viral particle having a modified cell binding activity and also expressing a bioactive agent including interleukin-2.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Povey et al. and Hammarstedt et al. to express antiviral agent interleukin-2 by the teachings of Dropulic et al. to achieve the goal of site specific delivery of interleukin as an antiviral agent via the selection of altered tropism of viral particle.

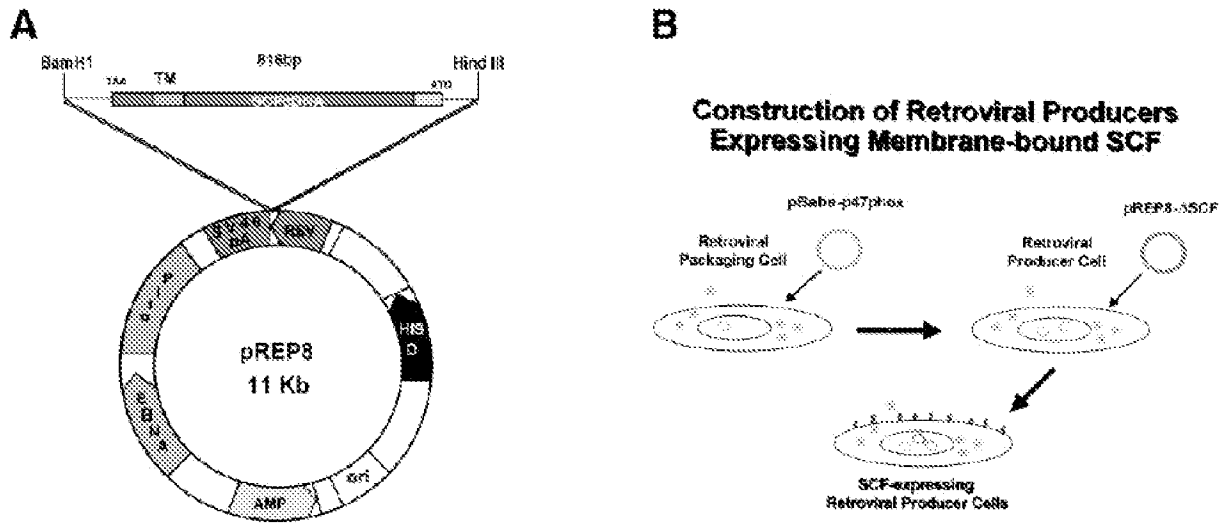
There would have been a reasonable expectation of success given (1) the generation of viral particle with altered tropism resulting from accelerated evolution of envelope genes by the teachings of Povey et al. and Hammarstedt et al., and (2) the expression of a cytokine from a viral vector by the teachings of Dropulic et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

11. Claims 43, 48, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Povey et al.** (Povey et al., Enhanced retroviral transduction of 5-fluorouracil-resistant human bone marrow (stem) cells using a genetically modified packaging cell line, *Blood*, 92(11):4080-9, 1998) in view of **Hammarstedt et al.** (Hammarstedt et al. Minimal exclusion of plasma membrane proteins during retroviral envelope formation. *Proc Natl Acad Sci U S A.* 97(13):7527-32, 2000) and **Guber et al.** (U.S. patent No. 569,177, issued Nov. 25, 1997; listed

in the PTO-892 in Non-Final rejection mailed on 09/05/2006). *This rejection is necessitated by the claim amendments of claim 43.*

Povey et al. teaches constructed a retroviral producer line (1MI-ΔSCF) that expresses the membrane-bound form of human stem cell factor (SCF) on its cell surface (See bridging paragraph, pages 4081-4082, and Figure 1, provided below, Povey et al., *Blood*, 92(11):4080-9, 1998).



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Povey et al. the retroviral transduction frequency of the quiescent 5-fluorouracil (FU) resistant bone marrow cells using the SCF-expressing producer line averaged about 20%, whereas those transduced using the retroviral particle obtained from parent producer line showed evidence of reduced levels or no transduction (See page 4084 and Figure 3, Povey et al., *Blood*, 92(11):4080-9, 1998).

Povey et al. does not explicitly teach that the SCF (i.e. a passenger peptide binding moiety encoded by exogenous nucleic acid recited in claim 43 of instant application) is allowed

to be incorporated into the viral particle, which in turn may account, at least in part, for the increased retroviral transduction frequency using the SCF-expressing producer line.

However, Hammarstedt et al. teaches that the retrovirus forms its envelope by budding at the plasma membrane (PM), and this process is primarily driven by its cytoplasmic core-precursor protein, Gag, as shown by the efficient formation of virus-like Gag particles in the absence of its envelope protein, Env. Hammarstedt et al. teaches the purification of Moloney murine leukemia virus Gag particles by sedimentation in an iodixanol gradient and donor PMs by flotation in a sucrose gradient and compared their protein compositions at equal lipid basis, and found that most PM proteins are present at similar density in both membranes. Hammarstedt et al. teaches the inclusion of PM proteins was unaffected by incorporation of Env protein into the envelope of the Gag particles and whether these were produced at high or low level in the cells. Hammarstedt et al. concludes that these findings indicate that most PM proteins become incorporated into the retrovirus envelope without significant sorting, and this feature of retrovirus assembly should be considered when studying retrovirus functions and developing retrovirus vectors.

The teachings by Hammarstedt et al. indicates that the retroviral particles produced from the SCF-expressing producer line taught by **Povey et al.** inherently allow the SCF, expressed on the plasma membrane of the retroviral packaging cell, to be incorporated into the retroviral particles when the viral particle buds from the retroviral packaging cell, as recited in claim 43 of instant application.

Neither Povey et al. nor Hammarstedt et al. teaches additional nucleic acid which can express any one of the bioactive agent, which is an enzyme, including thymidine kinase and cytosine deaminase, capable of converting a relatively non-toxic pro-drug into a cytotoxic drug.

With regard to claims 43, 48, and 52-53, Guber et al. teach recombinant retroviruses expressing a protein that converts a pro-drug into a cytotoxic agent (See title and abstract). Specifically, Guber et al. teaches the expression of a nucleoside kinase thymidine kinase (See claims 6-8, 22-23) that converts a purine-based or pyridimine-based drug with little or no cytotoxicity into a cytotoxic drug (See claim 5)

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Guber et al. to express a thymidine kinase that converts a pro-drug into a cytotoxic drug into the combined teachings of Povey et al. nor Hammarstedt et al. regarding the method of generating a retrovirus with altered tropism and to achieve the claims 52 and 53 of instant application regarding a method of making a retroviral particle having a modified cell binding activity and also expressing a bioactive agent such as thymidine kinase capable of converting a relatively non-toxic pro-drug into a cytotoxic drug.

One having ordinary skill in the art would have been motivated to modify the retroviral vector by the teachings of Povey et al. and Hammarstedt et al. to express thymidine kinase by the teachings of Guber et al. to achieve the goal of site specific delivery of thymidine kinase to a desired cell target for converting a pro-drug into a cytotoxic drug via the binding specificity of altered tropism of virus as taught by Povey et al. nor Hammarstedt et al.

There would have been a reasonable expectation of success given (1) the generation of viral particle with altered tropism resulting from accelerated evolution of envelope genes by the

teachings of Povey et al. and Hammarstedt et al., and (2) the expression of thymidine kinase converting a pro-drug into a cytotoxic drug from a recombinant retroviral vector by the teachings of Guber et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

12. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632